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An Assessment of Noninvasive Measurements of Arterial Compliance

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By
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A thesis submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirement for the degree of Masters in Clinical Research in the College of Graduate Studies.

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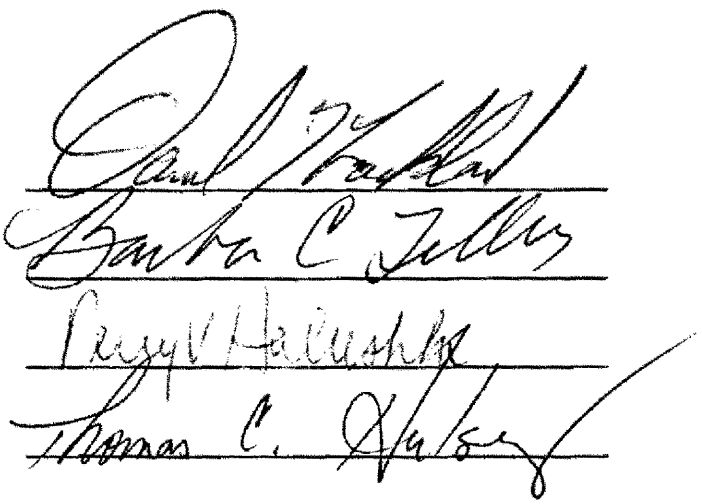

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Abstract

Arterial stiffness is considered both a risk factor and indicator of cardiovascular disease. The purpose of this study was to examine the associations of cardiovascular risk indicators of arterial compliance among 226 black and white individuals enrolled in an outpatient clinical setting. Data were collected by survey and examination with a computerized arterial pulse waveform analyzer. Arterial stiffness was estimated by indirect estimates of small artery and large artery compliance, as well as pulse pressure. After adjustments for age, race, and gender, logistic regression identified hypertension, end organ damage, and overweight as the strongest predictors for the three arterial stiffness indices. The results of this study identified similar factors associated with each of the different noninvasive measures of arterial stiffness.

Keywords: arterial compliance, pulse pressure, cardiovascular disease

Abbreviations:
CVD – Cardiovascular Disease
C1 – Large arterial elasticity
C2 – Small arterial elasticity
HDI – Hypertension Diagnostics, Inc
LAEI – large artery elasticity index
SAEI – small artery elasticity index
PP – pulse pressure
BP – blood pressure
BMI – body mass index

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Chapter 1

Introduction

One of the leading causes of mortality and a significant risk factor for Cardiovascular Disease (CVD) is the progression of atherosclerosis. Atherosclerosis includes the degenerative hardening of the arteries due to cholesterol-laden plaque accumulation narrowing the arterial wall, causing loss of elasticity. The loss of arterial elasticity and enhanced wave reflection are considered to be both markers of and an independent risk factor of CVD, suggesting a focus on arterial wall health in the prevention and treatment of this disease (Cohn J, 2001; Southerland et al. 2000; Van Doormnum et al. 2003). The transformation in arterial wall elasticity can be monitored and may help identify at risk patients and improve therapeutic decision making, due to slow progressive changes in the viscoelastic properties of the arterial wall long before the onset of disease symptoms (London G and Cohn J, 2002; Taal et al. 2007).

Arterial compliance is a measure of the storage capability of the blood vessel. Presently there is no "gold standard" to measure vessel compliance; most of the methods used in previous years have been invasive techniques, which are not ideal in the clinical setting. A developing and novel approach is the assessment of arterial pressure waveform, a technique based on noninvasive measurements of pulse contour analysis which allows the estimation of arterial elasticity and flexibility (Resnick et al. 2000).

A more traditional indirect measurement of arterial stiffness is the pulse pressure width, which is thought to be a cardiovascular risk factor in itself (Alderman et al. 1998; Arnett et al. 1994). Pulse pressure is the difference between the systolic and diastolic blood pressures, and is dependent on cardiac output, large arterial elasticity, and wave reflection (Nichols W, 2005; Syeda et al. 2003). Wide pulse pressures are markers of

increased vascular stiffness due to the loss of elastic recoil mechanism in the aorta; often occurring linearly with age (Burt et al. 1995).

Arterial stiffness is a predictor of cardiovascular events independent of traditional risk factors such as hypertension, diabetes, hypercholesterolemia, and stroke (Roman et al. 2005). The associations of arterial stiffness and disease outcome may be due to both a clinical and biological mechanism. However, it is unclear if disease progression can be attributed to the estimates determined from these non-invasive measures. This study includes measurements of small and large arterial stiffness as well as a traditional measure of pulse pressure in individuals with varying degrees of disease of end organ disease.

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Chapter 2

Review of Literature

Historical Overview

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the US, affecting more than 80 million Americans each year, and costs this country approximately $350 billion per year (AHA). One of the main risk factors for CVD is the progression of atherosclerosis (Elter, JR, *et al.*, 2006). Atherosclerosis is the degenerative hardening of the arteries due to cholesterol-laden plaque accumulation, narrowing the arterial wall, causing loss of elasticity. Inflammation is a key component of atherosclerosis and vascular endothelial cell damage due to the production of circulating cytokines (Van Doornum, *et al,* 2003). Atherosclerosis is a slow progressive disease that does not have immediate symptoms and thus many at risk individuals are unaware of their disease state. Often the first indicator of this disease is a fatal acute myocardial infarction (Naghavi et al, 2006).

The arterial wall consists of three layers: the intima, media, and adventitia. The intima is the inter-most surface of the arterial wall and is comprised mainly of endothelial cells, which normally resist adhesion of monocytes. When the endothelial cells are compromised they promote attachment of leukocytes due to the over expression of adhesion molecules, such as Vascular adhesion molecule-1(VCAM-1), interleukin-1 (IL-1), and tumor necrosis factor-α (TNF- α); which binds leukocytes that are found in the composition of plaque. This process is highly influential in the progression of inflammation. These monocytes migrate through the intima and mature into macrophages, which causes accumulation of cholesterol esters, forming foam cells producing a fatty streak. The media is comprised of smooth muscle cells (SMC), elastin, and collagen fibers, which are ultimately responsible for vessel constriction. Early stages

of atherogenesis leads to the development of 'complex plaque' due to the migration of SMC from the media to the intima, where fibro-lipid lesions are produced in the intima forming fibrous cap and necrotic core. The outer-most layer, adventitia, is comprised of fibrous connective tissue which maintains the vessel shape. Physical disruption of the lesion causes thinning and fracturing of the fibrous cap causing plaque rupture which leads to thrombus formation (Paquette et al, 2000; Augst et al 2007; Hashimoto et al 1999; Beck et al 2005; Booth et al, 2004).

Studies suggest that chronic inflammatory diseases and conditions may lead to an increased procoagulant state in the peripheral blood; which suggests that the same "systemic" markers associated with various vascular disease states may also be associated with cardiovascular disease and causally with atherosclerosis, myocardial infarction, stroke, and thrombosis (Loos, BG *et al*, 2005). These similar parameters may be involved with the atherosclerosis process in different organs throughout the body. Therefore, we can attempt to conclude that these same markers found in the peripheral blood may provide a biologically plausible explanation to the epidemiological link between chronic blood diseases (Loos, BG, *et al*, 2005). The loss of arterial elasticity and enhanced wave reflection are not only thought to be markers of CVD, but also an independent risk factor for CVD, suggesting a focus on arterial wall health in the prevention and treatment of CVD (Cohn JN *et* al, 2001; Southerland JH, *et al*, 2006).

The loss of arterial elasticity and enhanced wave reflection are due to the pathophysiological changes in the blood vessel, affecting vascular endothelial function of both the small and large arteries leading to a reduction in arterial compliance which is known to be associated with numerous cardiovascular events (Glasser et al 1997). This

transformation in arterial wall elasticity can be monitored and may help identify at risk patients and improve therapeutic decision making, due to slow progressive changes in the viscoelastic properties of the arterial wall long before the onset of disease symptoms (Glasser et al, 1997).

Vascular wall dynamics can be examined in a variety of ways. Arterial stiffness refers to resistance in deformation of the vessel wall. Arterial compliance is a measure of the storage capability of the blood vessel, and is defined as absolute change in volume, diameter, and area per change in pressure. Another common assessment is arterial distensibility which is the percent change in arterial compliance. Distensibility allows one to compare vessels of different sizes. Lastly, arterial elasticity, based on elastic modulus, describes the change in stress, or force per unit area, for a given change in strain, the ratio of change in area to the initial area. This measurement is independent of size and shape, and is used to assess vessel stiffness (Glasser et al, 1997).

Presently there is no "gold standard" to measure arterial compliance. Most of the methods used in previous years have been invasive techniques, which are not ideal in the clinical setting. There are three suggested mechanism to measure both large and small arterial compliance; which include last systolic pressure augmentation, biopsy of an isolate section of the small artery, and recently and most importantly assessing the arterial pressure waveform. This technique is based on a noninvasive measurement of pulse contour analysis which allows estimation of arterial elasticity and flexibility (Resnick et al 2000; Finkelstein et al, 1988).

The HDI/Pulsewave CR-2000 Research Cardio Vascular Profiling System, (Hypertension Diagnostics, Inc, Eagan, Minnesota, USA, 2001) can be used to evaluate

arterial compliance through a computerized arterial pulse waveform analysis, that calculates the diastolic decay of the pulse wave, which allows for inferences of vasculature resistance along with stroke volume ejection and systemic vascular resistance in the arterioles (Syeda et al, 2003; Nichols, 2005). This user friendly device computes arterial compliance by measuring response voltage from applied mechanical stress and/or strain over an electric field over the radial artery. The best possible explanation of waveform analysis is based on the modified Windkessel model in electrical terms (Glasser et al. 1997) (Figure 1). This model has two main parallel components, a resistor and a capacitor, representing the small and large arterial compliance, which is connected to a voltage source. This voltage source represents the left ventricle of the heart, which conducts blood flow into the system during systole creating proximal arterial pressure in the large vessels. This pressure is considered the pulsatile flow which defines the forward and reflecting waves due to stroke volume ejection into the aorta which is dependent on the compliance of the artery. This computerized method uses the arterial pressure to estimate capacitive compliance in the aorta, which represents the central determinant of systemic arterial compliance (SAC), C1, and is therefore a marker for large arterial stiffness. The interance element represents the inertia of the blood to the smaller blood vessels, where the oscillatory compliance is measured representing the distal pressure of the continuous, steady state flow across the small arteries. The brachial artery is the determinant of the peripheral arterial compliance (PAC), C2, and therefore is a marker for small artery elasticity (SAE). These measurements are collectively considered the diastolic decay of the pulse wave, which allow for inferences of vasculature resistance along with stroke volume ejection and systemic vascular resistance

(SVR) in the arterioles (Cohn et al, 2001; Glasser et al, 1997; Syeda et al, 2003; Nichols, 2005).

A more traditional indirect measurement of arterial stiffness is the pulse pressure width, which is thought to be a cardiovascular risk factor in itself. Pulse pressure is the difference between the systolic and diastolic blood pressure, and is dependent on cardiac output, large arterial elasticity, and wave reflection. Arterial stiffness due to structural changes in the arterial walls causes an increase in pulse wave velocity, and thus an increase in pulse pressure (Roman, MJ *et al.*, 2005). This increase in pulse pressure is due to the decrease in diastolic blood pressure which leads to myocardial ischemia and CVD. Systolic blood pressure increases linearly with age; however, diastolic blood pressure increases until around the age of 55, and then begins to decrease. This is due in part, to the loss of compliance, leading to a widening of the pulse pressure. Systolic hypertension and widen pulse pressure are markers of increased vascular stiffness due to the loss of elastic recoil mechanism in the aorta. When this loss occurs, the full stroke volume delivery through the resistance arterioles occurs during systole, instead of through a smooth steady flow throughout diastole. This widening effect of pulse pressure is a predictor of cardiovascular events (Burt *et al*, 1995).

Reduction in arterial compliance leads to a disproportionate increase in systolic blood pressure in the ascending aorta (Nichols, WN, 2005). Decreased compliance has two main adverse effects on central circulation: First the aorta stiffens and a blood injection from the left ventricle generates a pressure wave. The amplitude of this pulse pressure is higher in the aorta than in the left ventricle due to increased impedance. Second, there is an increase in systolic pressure due to early wave reflection causing a

decrease in diastolic blood pressure. (Rietzschel, ER *et al*, 2001). Both the systolic and pulse pressures become increased due to an alteration in the timing of reflected waves (Roman, MJ *et al.*, 2005). This ultimately causes an increase in arterial pressure wave velocity which is an indicator of arterial stiffness (Vlachopoulous, C *et al*, 2005).

Arterial stiffness is a predictor of cardiovascular events independent of traditional risk factors such as hypertension, diabetes, hypercholesterolemia, and smoking (Roman, MJ *et al.*, 2005). The relationship between atherosclerosis and inflammation is quite evident according to the current literature, it was also suggested by Yasmin *et al.* that elevated levels of inflammatory mediators may be strongly associated with arterial stiffening. This study reported that C-reactive protein may be independently related to higher pulse wave velocity and pulse pressure which are known surrogates of loss of arterial elasticity (Yasmin, MCM, *et al.*, 2004).

Contemporary Related Studies

Current literature suggests both a clinical and biological causal mechanism may exist to explain the potential association between chronic systemic diseases and cardiovascular disease progression. However, current evidence is insufficient to support the idea that systemic inflammation is an individual risk factor for cardiovascular disease. It is important to study the interrelationship between end organ diseases due to the large volume of people who are simultaneously, chronically affected by multiple inflammatory diseases. Even a small association between disease states would be vital information for the dental, diabetic, and especially the cardiovascular disease community. There are many pharmacological and non-pharmacological therapies available to prevent and reduce the severity of atherosclerosis and the events associated with CVD.

Some studies suggest that males have a higher burden of cardiovascular disease events as well as a higher burden of other blood related diseases, such as periodontal disease (Desvarieux, M *et al*, 2004). Thus, it is important to examine gender differences, along with possible race and/or ethnic differences when studying the relationship between systemic diseases and atherosclerosis. When examining the Atherosclerosis Risk In Communities (ARIC) study population, the investigators suggest that estrogen may play a protective role against vessel stiffness in premenopausal women. When compared to postmenopausal women, premenopausal women had less arterial stiffness, even when compared to men of the same age range (Arnett et al, 1994; Glasser et al 1997). Benetos *et al* showed that women tend to have a 5-10% lower stiffness than men of the same age.

Atherosclerotic progression occurs with the aging process, but the rate is accelerated with comorbid condition including high blood pressure, high cholesterol, smoking, and diabetes. Nearly all studies measuring vascular stiffness and reduced compliance have shown age as an intrinsic component of increase stiffness (Weinberger et al, 2002). Benetos *et al*, demonstrated this in subjects over the age of 50, in which a rapid increase in SBP and decrease in compliance was discovered, along with a plateau effect of the DBP; which continually decreased with age. Additional studies showed that with each decade increase in age, arterial stiffness increases by approximately 10-15% after the age of 10 in both males and females (Benetos et al, 2002).

Hypertensive individuals have stiffer, less compliant arteries than normotensive individuals (Beck, JD *et al*, 2005). The adverse effect of hypertension results in ventricular hypertrophy of the medial layer. In younger hypertensive patients, elevated BP does not affect the vasculature width in the radial artery, however, in central arteries the width increases proportionately with BP levels. In elderly hypertensive populations, arterial stiffening is primarily due to the development of plaque in the arteries independent of BP levels. Even in elderly hypertensives, vessel width only changes in the central arteries. In the Hypertension Detection and Follow-up Program, Alderman *et al* found elevated relative risk of 5-yr mortality with DBP, SBP, and pulse pressure in this hypertensive population. Even after adjusting for additional covariates, pulse pressure was found to be a significant predictor of overall mortality and is considered an independent predictor of cardiovascular disease events. (London et al, 2002). The Framingham study also depicted pulse pressure as a strong predictor of CVD more

specifically of myocardial infarction in both hypertensives and normotensives (Benetos et al, 1997; Benetos et al, 1998).

Fasting glucose is also known to be highly associated with arterial stiffness, proportionately with level of blood glucose, even among normal healthy subjects. Hyperglycemia is a common factor for both Type 1 and Type 2 diabetic individuals, and has been shown to be associated with an increase in arterial stiffness when compared to non-diabetic individuals, even though many other factors including disease duration and degree of therapy control are thought to influence this affect as well.

In vitro studies have shown a link between arterial stiffness and hypercholesterolemia along with clinical studies suggesting a significant positive correlation between cholesterol and low-density lipoprotein cholesterol (LDL), and a negative correlation with high-density lipoprotein cholesterol (HDL) with arterial stiffness. Familial hypercholesterolemia has also been shown to be associated with the stiffening of the arterial wall; which implies possible genetic and environmental components may play an essential role in the development of arterial stiffness and atherosclerosis.

Additional studies have shown impaired arterial flexibility especially in the aortic, carotid, iliac, and brachial arteries in patients with congestive heart failure (CHF). Arterial stiffness has been shown to be causally related to increase of SBP and pulse pressure in patients with End-stage Renal Disease (ESRD) and is an independent risk factor for CVD related morbidity and mortality (Benetos et al, 2002).

Cigarette smoking is another known risk factor for atherosclerosis accelerating endothelial damage, possibly due to inhibited basal and nitric oxide (NO) production.

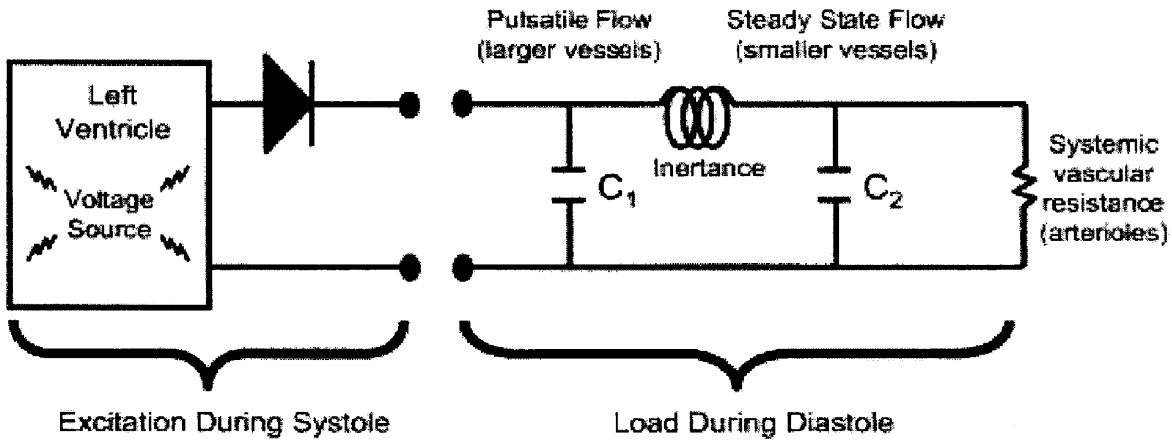
Cigarette smoking elevates blood pressure levels even at an acute level, and has been shown to decrease arterial compliance in both normotensives and hypertensive smokers compared to non-smokers.

Exercise has been shown to be associated with arterial compliance, but only in a few studies; in which they illustrated exercise training caused an increase in arterial compliance contributed to enhanced maximal oxygen consumption (Glasser et al, 1997).

Significance

The relationship of atherosclerosis and "systemic" disease is unclear particularly among whites and blacks. This study implements a novel measurement of arterial stiffness as well as a traditional measure of pulse pressure in a dental health population with individuals with varying degrees of disease of different organs throughout the body. The results can be used to identify common factors in the mechanism of atherosclerosis as well the results will identify dental, diabetic, endocrine, and hypertension professionals as an important component of cardiovascular disease prevention. This study will assign the risks of multiple indicators of arterial stiffness with hypertension, hypercholesterolemia, end organ damage, and overweight in black and white men and women. Early detection of atherosclerotic markers in high risk individuals may prove to be opportunistic in identifying cardiovascular events that may also be progressing along with other comorbid diseases (Morrison *et al*, 1995).

Figure 1. Electrical schematic of the modified Windkessel model of the vasculature.



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Chapter 3

Manuscript

Planned Submission to: Therapeutic Advances in Cardiovascular Disease

Manuscript

Title:
An assessment of noninvasive measurements of arterial compliance.

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Abstract

Arterial stiffness is considered both a risk factor and indicator of cardiovascular disease. The purpose of this study was to examine the associations of cardiovascular risk indicators of arterial compliance among 226 black and white individuals enrolled in an outpatient clinical setting. Data were collected by survey and examination with a computerized arterial pulse waveform analyzer. Arterial stiffness was estimated by indirect estimates of small artery and large artery compliance, as well as pulse pressure. After adjustments for age, race, and gender, logistic regression identified hypertension, end organ damage, and overweight as the strongest predictors for the three arterial stiffness indices. The results of this study identified similar factors associated with each of the different noninvasive measures of arterial stiffness.

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Introduction

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increased vascular stiffness due to the loss of elastic recoil mechanism in the aorta; often occurring linearly with age [Burt et al. 1995].

Arterial stiffness is a predictor of cardiovascular events independent of traditional risk factors such as hypertension, diabetes, hypercholesterolemia, and stroke [Roman et al. 2005]. The associations of arterial stiffness and disease outcome may be due to both a clinical and biological mechanism. However, it is unclear if disease progression can be attributed to the estimates determined from these non-invasive measures. This study includes measurements of small and large arterial stiffness as well as a traditional measure of pulse pressure in individuals with varying degrees of disease of end organ disease.

Methods

Study Population

This study is a cross-sectional assessment of 226 subjects from a dental health clinic at the Medical University of South Carolina, as well as a local independent retirement community. All data were previously collected information from health surveys and pulse contour analysis. The 33 question self-report survey was conducted by an interviewer which included demographic information, socioeconomic status information, and medical history.

Measurements of Arterial Compliance

This study includes three measurements that estimate arterial stiffness in black and white men and women with varying degrees of CVD related risk factors, including hypertension, hypercholesterolemia, and body mass index (BMI). The HDI/Pulsewave CR-2000 Research Cardio Vascular Profiling System, (Hypertension Diagnostics, Inc,

Eagan, Minnesota, USA, 2001) was used to evaluate arterial compliance through a computerized arterial pulse waveform analysis, that calculates the diastolic decay of the pulse wave, which allows for inferences of vasculature resistance [Finkelstein et al. 1991; Zimlichman et al. 2005]. Arterial compliance is defined as absolute change in volume, diameter, and area per change in pressure. This computerized model uses arterial pressure to estimate capacitive compliance in the aorta, which represents the central determinant of systemic arterial compliance, C1; and is therefore a marker for large arterial stiffness (LAEI). Oscillatory compliance is measured in the brachial artery, the determinant of the peripheral arterial compliance, C2; and is thus a marker for small artery stiffness (SAEI). The best possible explanation of waveform analysis is based on the modified Windkessel model [Glasser et al. 1997].

Cardiovascular profile measurements were taken with the subject in supine position from the upper right arm by a blood pressure cuff and left radial artery by a pulse pressure sensor.

Large Arterial Elasticity Index (LAEI), Small Arterial Elasticity Index (SAEI), and Pulse Pressure (PP) were used to compare those with and without cardiovascular related risk factors, including hypertension, hypercholesterolemia, end organ damage, and being overweight. The distribution of the data was examined and subjects were considered to be 'high risk' for reduced arterial compliance if they were included in any of the three upper quartiles of LAEI, SAEI, or PP. An Arterial Stiffness Score of 0-3 was assigned to each subject based on the number of upper quartiles in which the subjects were stratified.

Subjects were considered to have end organ damage if they had a history of diabetes, stroke, heart disease, myocardial infarction, kidney disease, or lung or leg vein blood clots.

Cardiovascular disease risk was also determined from systolic BP, diastolic BP, body mass index (BMI), pulse pressure (PP), and mean arterial blood pressure.

Data Management and Statistical Analysis

Data are reported as frequencies for categorical variables and means ± standard deviation for continuous variables. Pearson's Correlations were used for continuous variables and Chi-squared proportions were used for categorical variables to compare risk factors and hemodynamic parameters. Multivariable cross-sectional modeling using binary logistic regression was used to estimate odds ratios and 95% confidence intervals for CVD outcomes by Arterial Stiffness Score categories. Statistical analyses were conducted using SAS analysis software, and were considered statistically significant at the .05 level.

Results

Compliance Measurements

Assessments were completed on 226 dental clinic subjects. The compliance parameters in relation to risk factors and demographic characteristics of the subjects are provided in Table 1. The mean Large Arterial Elasticity Index (LAEI) was 13.4 ± 5.35 mL/mmHg x 10, mean Small Arterial Elasticity Index (SAEI) was 4.9 ± 3.9 mL/mmHg x 100, mean pulse pressure (PP) was 60.8 ± 25.9, and the mean age was 60.5 ± 15.6 in the total study cohort. No differences in LAEI, SAEI, or PP were detected between white

and black subjects, between subjects with and without hypercholesterolemia, or between smokers and non-smokers (Table 1).

Female subjects had significantly greater reductions in both LAEI ($p < .0001$) and SAEI ($p = .002$) but no difference in PP when compared to male subjects. Subjects with BMI greater than 25 were found to have significantly reduced LAEI ($p = .004$). Whereas subjects with end organ damage had significantly reduced LAEI ($p = .01$) and SAEI ($p = .007$) (Table 1).

Patients older than 60 years of age showed a significant reduction in LAEI ($p < .0001$), SAEI ($p < .0001$), and PP ($p = .02$). It is known that the arterial elastic recoil function is reduced significantly after the age of 60 and thus we would expect to see a reduction in the small and large arterial compliance as well as with pulse pressure measurements due to this age-related physiological change in vessel function [Izzo J and Black H, 1999]. Subjects with hypertension also showed a significant reduction in LAE ($p < .0001$) and SAE ($p < .0001$), and a slight reduction in PP ($p = .09$) when compared to subjects without hypertension (Table 1).

LAEI and SAEI compliance parameters were highly statistically correlated ($p < .0001$) with a Pearson's correlation coefficient of 0.358 (-0.095, 0.164). This was to be expected because both the small and larger arterial elasticity indices were measured using the same mechanism on two different vessels. The LAEI and PP parameters were inversely correlated ($p = 0.04$) with a Person's coefficient of - 0.141 (-0.266, -0.011). As the large arteries become more rigid the pulse pressure increases, resulting in an inverse relationship between these two parameters. However, the SAEI and PP parameters were not significantly correlated.

Each of the 226 participants was assigned an arterial stiffness score based on placement in upper quartiles of the three arterial stiffness indices. Over half (57.5%) of the participants had a score of 0 (Table 2). The prevalence decreased with each score category, 22.1% with a score of 1, 11.1% with a score of 2 and 9.3% with a score of 3 (Table 2).

Associations with Level of Vessel Disease (Arterial Stiffness Score)

Table 3 presents the association of age, gender, race, and arterial stiffness score with hypertension, hypercholesterolemia, end organ damage, and overweight. Age was significantly associated with hypertension, hypercholesterolemia, and end organ damage with greatest risk in age greater than or equal to 60 years. Males and blacks were significantly more likely to be overweight than their female and white counterparts. Hypertension and end organ damage increased significantly with arterial stiffness score.

The crude and adjusted odds ratios for hypertension, hypercholesterolemia, end organ damage, and overweight by arterial stiffness score are presented in table 4. No significant patterns were detected by the adjusted model. However, significant odds ratios were identified for hypertension and end organ damage for arterial stiffness score of 2.

Discussion

This cross-sectional study compared three indicators of vascular compliance estimated from non-invasive measurements with the calculations of a risk score based on the upper quartile in the three measures. Over half of the subjects had a score of 0, with 42.5% having a score of 1 or greater. While the majority of the study population was over 60 years of age and had one or more cardiovascular disease risk factors and end

organ damage, less than 10% had a score of 3. When comparing SAEI, LAEI, and PP as continuous measures, SAEI and LAEI were found to be significantly correlated with each other. This would be expected as both measures were estimated from the same pulse wave analysis. However, PP, also estimated from the same measurement was not associated with either SAEI or LAEI.

The analyses in this study identified similar factors associated with the three indicators of arterial stiffness. Age and hypertension were significantly associated with the highest risk measurements with each of the three. End organ damage and gender were associated with SAEI and LAEI but not with PP. The higher rates of stiffer arteries among women are consistent with other studies in that women tend to have a 5-10% lower stiffness than men of the same age [Benetos et al. 2002].

Atherosclerotic progression occurs with the aging process, but the rate is accelerated with comorbid conditions. Nearly all studies measuring vascular stiffness and reduced compliance have shown age as an intrinsic component of increase stiffness [Weinberger et al. 2002]. Benetos *et al* demonstrated with each decade increase in age, arterial stiffness increases by approximately 10-15% after the age of 10 in both males and females [Benetos et al. 2002]. We found significant associations between advanced vessel disease and age, especially among subjects greater than 60 years of age.

Hypertensive individuals have stiffer, less compliant arteries than normotensive individuals [Beck J and Offenbacher S, 2005; Benetos et al. 1997; Benetos et al. 1998]. In elderly hypertensive populations, arterial stiffening is primarily due to the loss of elastic recoil function in the arteries. In this study we found hypertension, end organ damage, and being overweight to be associated with arterial compliance estimates and

with Arterial Stiffness Score. After adjusting for age, sex and race, significant odds ratios for hypertension and end organ damage were only detected for individuals with a score of 2.

There are several limitations in this study. First, the information collected was from a self-report interviewer survey, which may have biased some of the parameters recorded, such as smoking status and diabetes. In addition, the drug and treatment information collected in this study was not complete or reliable.

The three indicator assessed arterial stiffness differently and at different parts of the body. One might expect different values given disease progression may be different. For example, disease progression and arterial compliance might be different in the small arteries as opposed to the large arteries and pulse pressure. Thus, disease might be detected earlier in the small arteries. However, these assessments did not detect such differences.

Early detection of atherosclerotic markers in high risk individuals may prove to be opportunistic in identifying cardiovascular events that may also be progressing along with other comorbid diseases [Morrison et al. 1995].

Conclusions

The three different indicators of arterial compliance had similar factors associated with the measurements. Likewise, the associations with disease outcomes were similar for the three measures. The arterial stiffness score summing the highest risk group was associated with the highest disease risk. These results identify one of the three assessments of arterial stiffness are associated with increased disease risks. However, the analyses failed to identify any one of the three measures as superior in predicating

disease. As the three indicators were determined from one measurement, each marker should be correlated. Future longitudinal studies are needed to determine if SAEI or LAEI is an independent predictor of CVD. Such studies should include measures of arterial stiffness prior to end-organ damage with follow-up.

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Table 1. Compliance parameters in relation to CVD risk factors (N = 226)			
CVD Risk Factors	LAEI	SAEI	PP
Age > 60 (n =119)	11.6 ± 5.1	3.5 ± 2.1	64.7 ± 14.3
Age < 60 (n =107)	15.5 ± 4.9	6.4 ± 4.8	56.3 ± 34.0
P value	<.0001	<.0001	0.02
Men (n = 99)	15.6 ± 4.6	5.8 ± 3.6	61.7 ± 35.4
Women (n = 127)	11.8 ± 5.3	4.1 ± 4.1	60.0 ± 14.8
P value	<.0001	0.002	NS
White (n = 184)	13.4 ± 5.4	4.9 ± 4.1	61.1 ± 27.8
Black (n = 41)	14.0 ± 5.0	4.7 ± 3.1	58.4 ± 13.3
P value	NS	NS	NS
Hypertension (n = 107)	11.9 ± 5.2	3.8 ± 2.4	63.8 ± 13.5
Not Hypertensive (n = 119)	14.9 ± 5.1	5.8 ± 4.7	58.0 ± 33.1
P value	<.0001	<.0001	0.09
Hypercholesterolemia (n = 98)	13.3 ± 5.7	4.5 ± 2.7	61.9 ± 13.3
Not Hypercholesterolemia (n = 128)	13.6 ± 5.1	5.1 ± 4.6	60.1 ± 32.4
P value	NS	NS	NS
End Organ Damage (n = 84)	12.3 ± 4.9	3.7 ± 2.1	63.2 ± 14.7
Not End Organ Damage (n = 142)	14.1 ± 5.5	5.5 ± 4.6	59.3 ± 30.6
P value	.01	.007	NS
BMI ≥ 25 (n = 160)	14.1 ± 5.5	4.9 ± 3.0	61.6 ± 29.5
BMI < 25 (n = 66)	11.9 ± 4.6	4.8 ± 5.5	58.6 ± 13.4
P value	0.004	NS	NS
Smoker (n = 9)	15.2 ± 4.0	5.9 ± 3.4	57.0 ± 6.7
Non-smoker (n = 217)	13.4 ± 5.4	4.8 ± 4.0	60.9 ± 26.3
P value	NS	NS	NS

SAEI = small arterial elasticity index (in mL/mmHg x 100); LAEI = large arterial elasticity index (in mL/mmHg x 10); PP = pulse pressure mmHg; NS = not significant; determined by Pearson's correlation p-value.

Table 2. Percentages of risk groups by Arterial Stiffness Score			
Arterial Stiffness Score	Upper Quartiles	Total Study (N=226)	Total Study %
0	None	130	57.5
1	LAE	16	7.0
	SAE	24	10.6
	PP	10	4.4
2	LAE*SAE	13	5.8
	LAE*PP	6	2.7
	SAE*PP	6	2.7
3	LAE*SAE*PP	21	9.3

LAE = large arterial elasticity index; SAE = small arterial elasticity; PP = pulse pressure; * = multiple upper quartiles.

Table 3. Distributions of CVD Outcomes by Arterial Stiffness Score, age, gender, and race. (N=226)					
		CVD Outcomes			
Model Covariates	**Total Study 226 (100 %)**	**Hypertension 107 (47%)**	**Hyper-cholesterolemia 98 (43%)**	**End Organ Damage 84 (37%)**	**Overweight 160 (71%)**
Age					
≥ 60	119 (53%)	78 (66%)	60 (50%)	63 (53%)	81 (68%)
< 60	107 (47%)	29 (27%)	38 (36%)	21 (20%)	79 (74%)
	p-value	*<0.0001*	*0.024*	*<0.0001*	*0.34*
Gender					
Male	99 (44%)	46 (47%)	50 (51%)	38 (38%)	77 (78%)
Female	127 (56%)	61 (48%)	48 (38%)	46 (36%)	83 (65%)
	p-value	*0.82*	*0.056*	*0.74*	*0.042*
Race					
White	184 (81%)	83 (45%)	75 (41%)	71 (39%)	121 (66%)
Black	41 (18%)	23 (56%)	22 (54%)	12 (29%)	38 (93%)
	p-value	*0.20*	*0.13*	*0.26*	*0.0006*
Score					
0	130 (58%)	46 (34%)	56 (43%)	36 (28%)	101 (78%)
1	50 (22%)	26 (52%)	21 (42%)	19 (38%)	32 (64%)
2	25(11%)	20 (80%)	8 (32%)	19 (76%)	15 (60%)
3	21 (9%)	15 (71%)	13 (62%)	10 (48%)	12 (57%)
	p-value	*<0.0001*	*0.23*	*<0.0001*	*0.0599*
Score = Arterial Stiffness Score; Overweight = BMI > 25; categorical variables are presented as counts (row %); *p-value* determined by Chi-square.					

Table 4. Odds Ratios and 95% Confidence Intervals for Cardiovascular Disease (CVD) outcomes by Arterial Stiffness Score		
	Crude Model	Adjusted Model §
CVD Outcomes by Arterial Stiffness Score	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Hypertension		
1	1.98 (1.02, 3.83)	1.02 (0.47, 10.33)
2	7.30 (2.57, 20.74)	3.25 (1.02, 5.83)
3	4.57 (1.66, 12.57)	1.88 (0.61, 1.10)
0	1.0	1.0
Hypercholesterolemia		
1	0.96 (0.49, 1.85)	0.64 (0.30, 1.37)
2	0.62 (0.25, 1.54)	0.36 (0.13, 1.03)
3	2.15 (0.83, 5.53)	1.36 (0.47, 3.94)
0	1.0	1.0
End Organ Damage		
1	1.60 (0.80, 3.18)	1.09 (0.50, 2.36)
2	8.27 (3.06,22.36)	4.92 (1.66, 14.59)
3	2.37 (0.93, 6.07)	1.32 (0.46, 3.82)
0	1.0	1.0
Overweight		
1	0.51 (0.25, 1.04)	0.47 (0.21, 1.05)
2	0.43 (0.18, 1.06)	0.44 (0.16, 1.25)
3	0.38 (0.15, 0.98)	0.38 (0.12, 1.15)
0	1.0	1.0
Reference group = score of zero; Overweight = BMI > 25; § Adjusted for Age, Gender, Race		

An Assessment of Noninvasive Measurements of Arterial Compliance.

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Chapter 4

Summary and Conclusions

The three different indicators of arterial compliance had similar factors associated with the measurements. Likewise, the associations with disease outcomes were similar for the three measures. The arterial stiffness score summing the highest risk group was associated with the highest disease risk. These results identify one of the three assessments of arterial stiffness are associated with increased disease risks. However, the analyses failed to identify any one of the three measures as superior in predicating disease. As the three indicators were determined from one measurement, each marker should be correlated.

This study was a hypothesis driving study to assess cardiovascular disease risk factors, especially hypertension and end organ damage in a local population cohort with varying disease states. The results from this study suggest that this noninvasive screening method could potentially be used in the clinical setting as an alternative diagnostic tool in regards to cardiovascular health. Pulse contour analysis should be further studied in a true clinical setting to examine the diagnostic and economical benefits of this noninvasive screening method. Future longitudinal studies are needed to determine if SAEI or LAEI is an independent predictor of CVD. This study allowed me to gain knowledge in cardiovascular disease health, especially in hypertension. I plan to continue my education in epidemiology with a focus in cardiovascular disease and hypertension research.

Acknowledgments

The project described was supported by Grant Number T32RR023258 from the National Center For Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health. The project was also funded in part by Black Pooling Project 1R01HL072377-01(DTL). We would also like to thank Dr Amal Rastogi for collecting the data used in this study.

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Appendices

Appendix A - Preliminary Study Sample Size

With a sample size of 226, approximately 19 and 107 subjects per group are needed for a two-sample, two-sided .10 significance level at a power of 80% with an effect size of 0.600 to detect an approximate 3 ml/mmHg clinically important difference (as reported in Woodman *et al*) in large arterial elasticity, C1 assuming a standard deviation of 5.0. Approximately 29 and 197 subjects per group are required for a two-sample, two-sided 0.10 significance level at a power of 80% with an effect size of 0.500 to detect an approximate 2 ml/mmHg clinically important difference (as reported in Woodman *et al*) in small arterial elasticity, C2 assuming a standard deviation of 4.0. Refer to **Table B** for sample size calculations.

Table B: Two group t-test of equal means (unequal n's)

	1	2
Test significance level, a	0.100	0.100
1 or 2 sided test?	2	2
Group 1 mean, m_1	14.900	5.800
Group 2 mean, m_2	11.900	3.800
Difference in means, $m_1 - m_2$	3.000	2.000
Common standard deviation, s	5.000	4.000
Effect size, $d = \|m_1 - m_2\| / s$	0.600	0.500
Power (%)	80	80
n_1	19	29
n_2	207	197
Ratio: n_2 / n_1	10.105	6.069
$N = n_1 + n_2$	226	226

Appendix B - Preliminary Studies

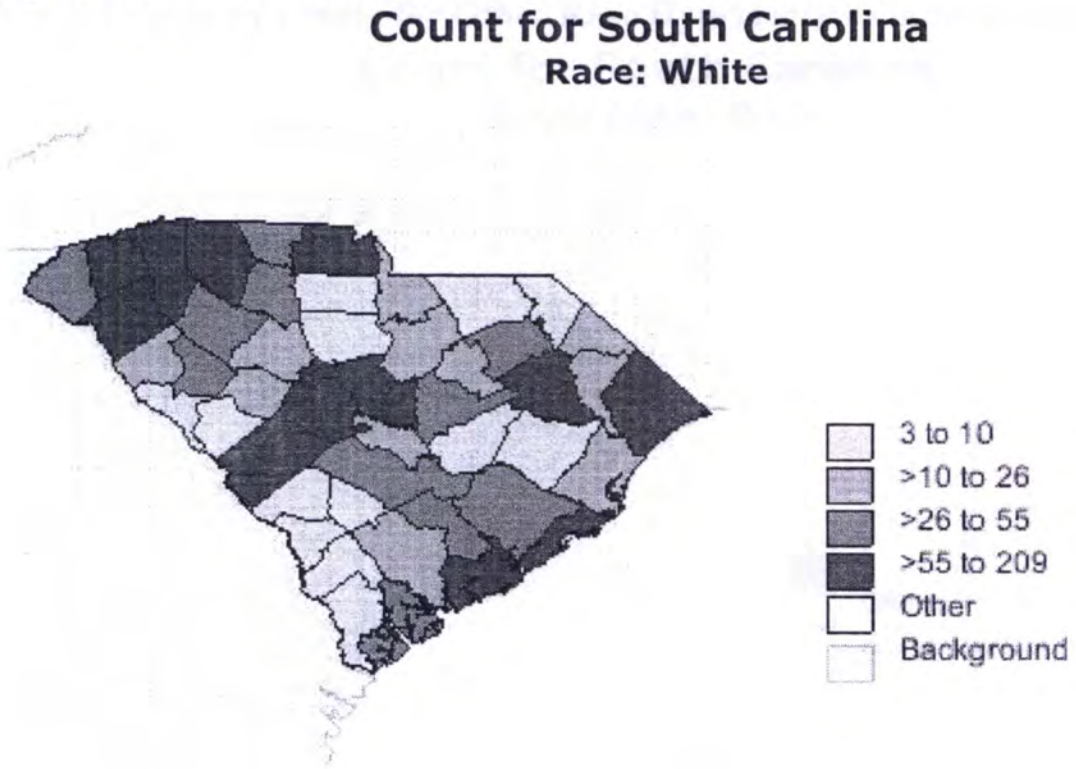
CDC Wonder was utilized to determine the mortality rate of hypertension based in the state of South Carolina from 1999-2003. The ICD-10 code used to identify hypertensive diseases were H110-H113, which includes essential hypertensive diseases, hypertensive heart disease, and hypertensive renal disease. Results were grouped by race. All genders, ages, races, and urbanizations were included. Rates were standardized to the 2000 US population. Age Adjusted Rates and Crude Rates Per 100,000 for all of the South Carolina counties, grouped by race (i.e. White, Other, Black or African American) are shown in **Table A**. The counts of the disease by race are also shown in **Table A**. **Maps 1, 2 and 3** display the same information geographically, grouped by county. The Age Adjusted Rates per 100,000 for Black or African American in South Carolina is 41.5, Whites is 13.1, and Other 1.7 (may be unreliable). The mortality rates of Blacks (African American) due to hypertension related diseases are drastically higher in South Carolina as compared to White and Other Races groups. As compared to the US mortality rate due to hypertension, South Carolina falls in the 36.8 to 44.7 per 100,000 range, which is considerably higher as compared to other states in the US. The most concentrated areas of mortality due to hypertension seem to be located in the southeastern regions including considerably higher rates from Georgia, Florida, to Texas. **Maps 4, 5**, and **6** display the Age Adjusted Rates for the US population for comparison to SC rates. (CDC Wonder, 2007).

Table A: Age Adjusted and Crude Rates per 100,000 in SC grouped by Race

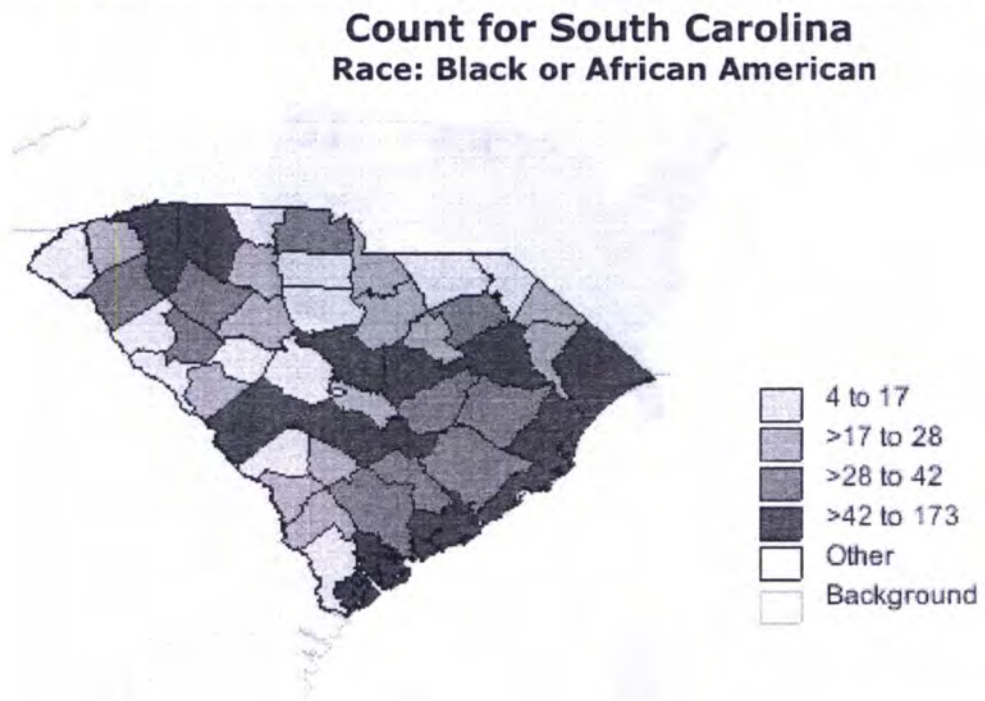
Race	State	Count	Population	Crude Rate per 100,000	Age Adjusted Rate per 100,000
White	SC (45)	1,888	13,941,393	13.5	13.1
Black/ AA	SC (45)	1,851	6,066,453	30.5	41.5
Other	SC (45)	4	294,649	1.4*	1.7*

*Number may be unreliable according to CDC Wonder

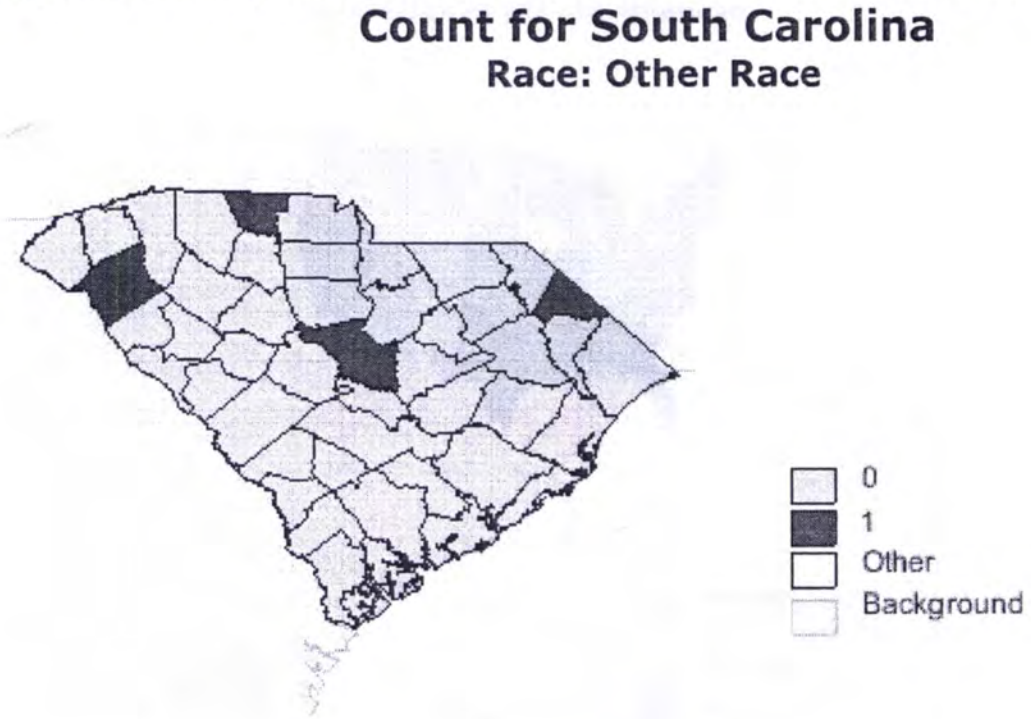
Map 1: Counts by county for White Hypertensives in SC



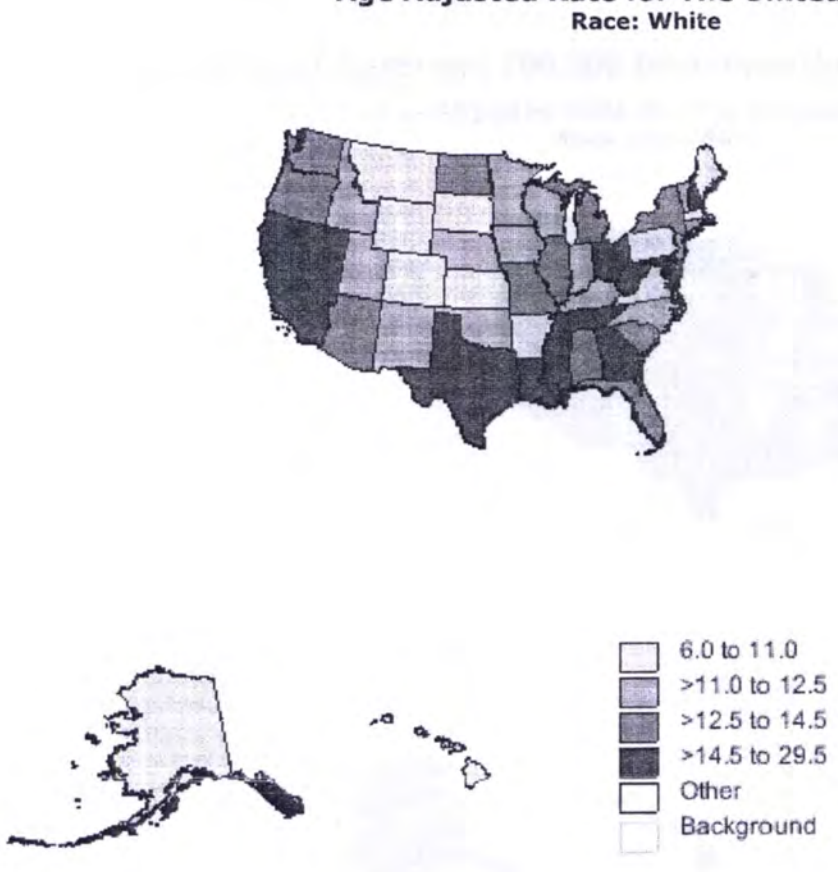
Map 2: Counts by county for Black/ African American Hypertensives in SC



Map 3: Counts by county for Other Race Hypertensives in South Carolina



Map 4: Age Adjusted Rates per 100,000 for White Hypertensives in the US



Appendix C - Subset Cohort Data

Subset Study Population:

A subset of 76 subjects had 25ml serum blood samples collected for a lipid profile to measure total cholesterol, LDL, HDL, white blood cell count (WBC), hemoglobinA1C, fibrinogen, triglyceride levels. All blood samples test were completed by MUSC, General Clinical Research Center (GCRC).

Results:

When examining the subset of subjects with blood sample analysis age, Hemoglobin A1C, High LDL greater than 160, HDL, Fibrinogen, and elevated fibrinogen above 300 was significantly correlated with arterial stiffness score (p-value <0.10); however, there was no association present with the various disease states in this subset population. Diabetes, kidney disease, and low HDL below 40 were significantly associated with arterial stiffness score (Table C).

Discussion:

In the subset population with lipid profiles, we found that Hemoglobin A1C, LDL above 160, HDL, and Fibrinogen above 300 was statistically associated with Arterial Stiffness Score, and could possibly be a another predictor of vessel disease and atherosclerosis diagnoses. Fasting glucose has been shown to be highly associated with arterial stiffness, proportionately with level of blood glucose, even among normal healthy subjects. Hyperglycemia is a common factor for both Type 1 and Type 2 diabetic individuals, and has been shown to be associated with an increase in arterial stiffness when compared to non-diabetic individuals, even though many other factors including disease duration and degree of therapy control are thought to influence this affect as well

(Lehmann, ED, *et al*, 1992). *In vitro* studies have shown a link between arterial stiffness and hypercholesterolemia along with clinical studies suggesting a significant positive correlation between cholesterol and low-density lipoprotein cholesterol (LDL), and a negative correlation with high-density lipoprotein cholesterol (HDL) with arterial stiffness. Familial hypercholesterolemia has also been shown to be associated with the stiffening of the arterial wall; which implies possible genetic and environmental components may play an essential role in the development of arterial stiffness and atherosclerosis (Cheng, HM, 2007).

Table C. Summary Statistics for blood samples (N=76)			
Parameters	**Total Population N=76**	**Pearson's P value**	**CHI-SQ P value**
Arterial Stiffness Score (1-3)	45 (59%)		
Age	57.1 ± 12.7	<.0001	
Gender (male)	38 (50%)	0.1539	0.1350
Race (white)	66 (87%)	0.6810	0.9124
Hypertension	32 (42%)	0.1114	0.2271
Diabetes	10 (13%)	0.2387	0.0652
Hypercholesterolemia	31 (41%)	0.3782	0.8119
Myocardial Infarction	6 (8%)	0.4889	0.2834
Stroke	6 (8%)	0.4889	0.2834
Heart disease	12 (16%)	0.3051	0.1518
Kidney problems	8 (11%)	0.5958	0.0343
Blood clots	3 (4%)	0.8824	0.3026
Overweight (BMI >25)	54 (71%)	0.2573	0.4136
HbA1C	5.53 ± 0.67	0.0922	
High HbA1C	4 (5%)	0.7156	0.2008
Total Cholesterol	193.88 ± 42.7	0.1259	
High Total Cholesterol	13 (17%)	0.1383	0.3690
LDL	118.42 ± 37.8	0.3047	
High LDL	12 (16%)	0.0673	0.1815
HDL	46.71 ± 15.6	0.0454	
Low HDL	29 (39%)	0.1083	0.0737
Triglycerides	149.03 ± 103.2	0.3697	
High Triglycerides	14 (19%)	0.7946	0.4120
Fibrinogen	354.58 ± 79.0	0.0338	
Elevated Fibrinogen	62 (82%)	0.0758	0.2168

* Data are expressed as frequencies for categorical variables and means ± standard deviation for continuous variables; HbA1C – Hemoglobin A1C; High HbA1C ≥ 7; High Total Cholesterol ≥ 240; High LDL ≥ 160; Low HDL < 40; High Triglycerides ≥ 200; Elevated Fibrinogen ≥ 300; Zero Smokers in Subset group.

Appendix D - Health Survey

HEALTH INTERVIEW

Study ID Number _____

Gender Male Female

Clinic/Location _____

Date of last periodontal exam ____/____/_____

What is your birth date? ____/____/_____

Height_____ Weight_____

How would you best describe your racial identity? Circle all that apply.

White Black Hispanic Asian Other

How many times a week do you exercise? _____

How many times a day do you brush your teeth? _____

How many times a day do you use dental floss? _____

When was your last visit to a dentist? Month_____ Year_____

Do you have a regular dentist or dental clinic? YES NO

Has a dentist ever told you that you have gum disease, periodontitis, or gingivitis?

YES NO DON'T KNOW

Have you ever undergone any treatment for gum disease?

YES NO DON'T KNOW

IF YES → Treatments done _____

Have you smoked at least 100 cigarettes in your lifetime? YES NO

On average, about how many cigarettes a day DO/DID you smoke? _____

How many years have you smoked? _____

Have you used chewing tobacco or snuff, such as Redman, Beechnut, Copenhagen, or Skoal, at least 20 times? YES NO

On average, about how many times a day DO/DID you use snuff or chewing tobacco?

_____

What is the usual number of alcoholic beverages you HAVE/HAD per week?

_____

How long ago was your last cup of coffee/tea/caffeinated beverage?

_____

Have you ever had a HEART ATTACK?

YES NO DON'T KNOW

IF YES → How many times? _____

How long ago? _____

Have you ever had a STROKE?

YES NO DON'T KNOW

IF YES → How many times? _____

How long ago? _____

Do you use aspirin on a regular basis? YES NO DON'T KNOW

YES → How many days a week are you taking aspirin? _____

What dosage do you take? _____mg

Has a doctor ever told you that you had any of the following:

Heart Disease YES NO DON'T KNOW

Kidney Problems YES NO DON'T KNOW

IF YES→List? _____

Rheumatic fever, faulty heart valve, or heart murmur? YES NO DON'T KNOW

Blood clots in the lung or in the leg veins? YES NO DON'T KNOW

Artificial joint replacement? YES NO DON'T KNOW

Which joint and date of most recent surgery? _____

High Blood Pressure or Hypertension? YES NO DON'T KNOW

IF YES:

Are you taking medicine for this? YES NO DON'T KNOW

IF YES→Names if known? _____

_____

_____

_____

High Blood Cholesterol YES NO DON'T KNOW

IF YES:

Are you taking medicine for this? YES NO DON'T KNOW

IF YES→Names if known? _____

_____

_____

Diabetes YES NO DON'T KNOW

IF YES:

Are you taking medicine for this? YES NO DON'T KNOW

IF YES → Insulin or Pills:_____

Was insulin your first diabetes medicine? YES NO DON'T KNOW

FOR WOMEN:

Did diabetes occur only during pregnancy? YES NO DON'T KNOW

What medications and/or supplements are you currently taking?

_____

_____

What is the highest degree or level of school you have completed?

No Schooling
Grades 1-8
Grades 9-11
Completed high school
Some college but no degree
Technical School Certificate
Associate degree (Junior College, e.g. AA, AS)
Bachelor's degree (e.g. BA, AB, BS)
Graduate or professional school

Are you currently employed outside the home? YES NO

Are you retired? YES NO

What is/was your usual occupation? _____

On this sheet is a list of income groups. Please circle which group best represents your total combined family income for the past 12 months. This includes the total income before taxes earned in the past ear by all family members living with you. Please include money from jobs, net income from business, farm or rent, pensions, dividends, welfare,

social security payments and any other money received by you or any other family member living with you.

Less than 5,000	16,000-19,999	35,000-39,999	100,000 or more
5,000-7,999	20,000-24,999	40,000-49,999	
8,000-11,999	25,000-29,999	50,000-74,999	
12,000-15,999	30,000-34,999	75,000-99,999	

To help pay for your medical care, do you now have: (circle all that apply)

HMO or other private insurance such as Blue Cross, Aetna, 1199 Fund, etc.
Medicare
Medicaid
Military or Veteran's Administration sponsored
None
Other: _____

Interview date _____/_____/_____

Health Interview Survey designed by Dr Amal Rastogi.

Appendix E – IRB Approval

This study was approved for Exempt Research/Quality Assessment Review by MUSC Institutional Review Board on 12/13/2007. HR number 17855. Expiration Date 12/13/2012.

An Assessment of Noninvasive Measurements of Arterial Compliance.

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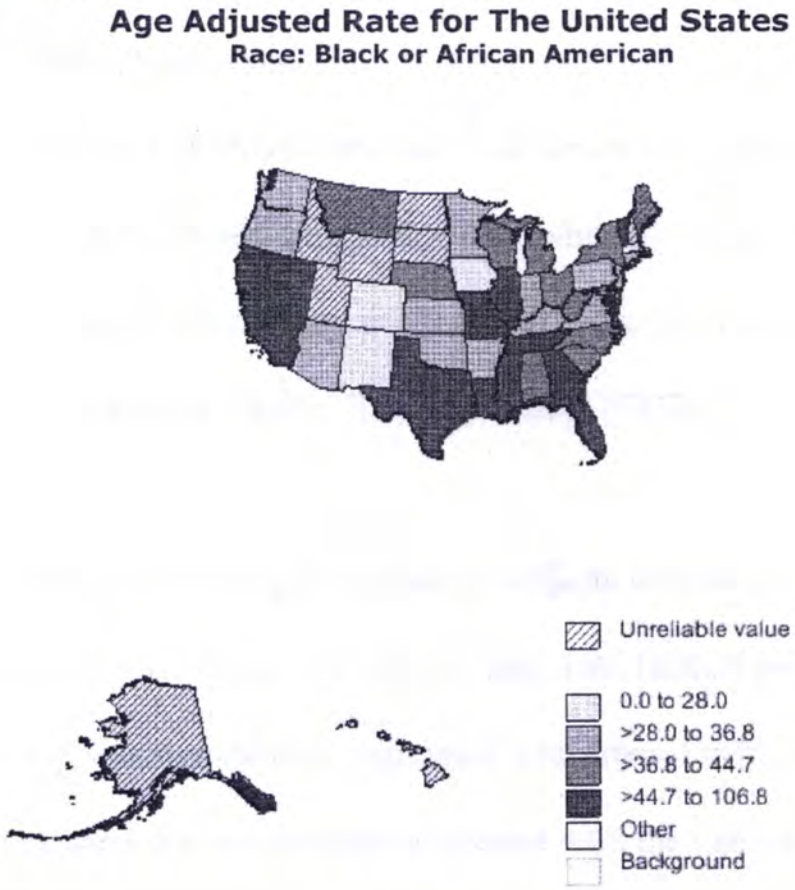
Map 5: Age Adjusted Rates per 100,000 for Black/AA Hypertensives in the US



Map 6: Age Adjusted Rates per 100,000 for Other Race Hypertensives in the US